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For:	**N-(Substituted Arylmethyl)-4-(Disubstituted Methyl) Piperidines and Piperazines**	**Atty:**	VLC/CMB

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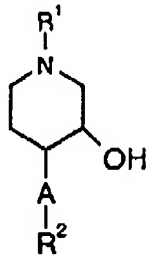
(54) Process for the production of substituted 3-hydroxypiperidines

(57) The present invention concerns a process for the preparation of a compound of formula 1 or a salt thereof



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characterised in that the process comprises

a) hydroboration of a compound of formula 2

in which formulae A is arylene; R^1 is $-C^*R^3R^4R^5$; R^2 is -O-alkyl, -O-cycloalkyl, -O-alkenyl, -O-aryl, -O-aralkyl, -O-aralkoxyalkyl, -O-alkylsulfonyl, -O-arylsulfonyl, chlorine, bromine or iodine; R^3 is hydrogen; R^4 is aryl; R^5 is alkyl, cycloalkyl, aryl, alkoxyalkyl or hydroxyalkyl; and wherein C* is an asymmetric carbon atom;

b) optionally followed by isolation of the desired stereoisomer.

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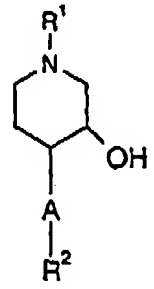
Description

[0001] The invention relates to a novel process for the preparation of substituted piperidines. More particularly the invention relates to the preparation of compounds of the formula 1



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and salts thereof, wherein

A is arylene;

R^1 is $-C^*R^3R^4R^5$;

R^2 is -O-alkyl, -O-cycloalkyl, -O-alkenyl, -O-aryl, -O-aralkyl, -O-aralkoxyalkyl, -O-alkylsulfonyl, -O-arylsulfonyl, chlorine, bromine or iodine;

R^3 hydrogen;

R^4 is aryl;

R^5 is alkyl, cycloalkyl, aryl, alkoxyalkyl or hydroxyalkyl;

and C* is an asymmetric carbon atom.

[0002] The compounds of formula 1 are new and can be used as chiral building blocks in the preparation of renin inhibitors especially disubstituted renin inhibitors as disclosed in WO 97/09311 e.g.1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine and (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine. The syntheses of optically active renin inhibitors via conventional resolution of racemates as disclosed in WO 97/09311 results in a considerable loss of product. The present invention provides a process avoiding the disadvantages of the above process.

[0003] According to the present invention the compounds of formula 1 above or salts thereof can be prepared by a process characterised in that it comprises

a) hydroboration of a compound of the formula 2

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in which formula
R^1, R^2 and A are defined as above;

b) optionally followed by isolation of the desired stereoisomer.

[0004] The term "alkyl" means alone or in combination a branched or unbranched alkyl group containing 1 to 8 carbon atoms, preferred 1 to 6 carbon atoms. Examples for branched or unbranched C_1-C_8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls, the isomeric octyls and preferred ethyl, n-propyl, and isopropyl and particularly preferred methyl.

[0005] The term "cycloalkyl" means alone or in combination a cycloalkyl cycle with 3 to 8 carbon atoms and preferred a cycloalkyl cycle with 3 to 6 carbon atoms. Examples for C_3-C_8 cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methyl-cyclohexyl, dimethyl-cyclohexyl and cycloheptyl.

[0006] The term "alkenyl" means alone or in combination alkenyl groups of 2 to 8 carbon atoms. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-ethyl-2-butenyl, and the like. Preferred is allyl.

[0007] The term "aryl" means alone or in combination a phenyl or a naphthyl group which can be substituted by one or several substituents chosen from alkyl, cycloalkyl, alkoxy, halogen, carboxy, alkoxycarbonyl, hydroxy, amino, nitro, trifluoromethyl and the like. Example of aryl substituents are phenyl, tolyl, methoxyphenyl, fluorophenyl, chlorophenyl, hydroxyphenyl, trifluoromethylphenyl, 1-naphthyl and 2-naphthyl.

[0008] The term "arylene" means alone or in combination a phenylene or a naphthylene group which can be additionally substituted by one or several substituents chosen from alkyl, halogen, nitro, cycloalkyl, alkoxy, hydroxy, amino, preferably alkyl, halogen and nitro. Examples for arylene are ortho-phenylene, meta-phenylene, para-phenylene, the tolylenes, methoxyphenylenes, fluorophenylenes, chlorophenylenes and naphthylenes. Preferred are phenylene, wherein the substituents of the phenylene which are defined by formula 1 are placed ortho, meta or preferred para to one another and wherein one or several additional substituents chosen from alkyl, halogen and nitro can be present at the arylene cyclus. Especially preferred substituents are methyl, chloro and nitro. Particularly preferred is unsubstituted phenylene and especially unsubstituted para phenylene.

[0009] The term "alkoxy" means alone or in combination the group -O-alkyl, wherein alkyl is defined as before. Examples are ethoxy, n-propyloxy, and iso-propyloxy. Preferred is methoxy.

[0010] The term "alkoxyalkyl" means alone or in combination an alkyl group, wherein a hydrogen is substituted by an alkoxy group. Examples are methoxymethyl, ethoxymethyl and 2-methoxyethyl. Particular preferred is methoxymethyl.

[0011] The term "aralkyl" means alone or in combination an alkyl group, wherein a hydrogen is substituted by an aryl group. A preferred example is benzyl.

[0012] The term "hydroxyalkyl" means alone or in combination an alkyl group, wherein a hydrogen is substituted by an hydroxy group. Examples are hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl. Preferred is hydroxymethyl.

[0013] The term "aralkoxyalkyl" means alone or in combination an alkyl group, wherein a hydrogen is substituted by an alkoxy group in which a hydrogen is substituted by an aryl group. A preferred example for aralkoxyalkyl is 3-(2-methoxy-benzyloxy)-propyl.

[0014] The term "alkylsulfonyl" means alone or in combination a sulfonyl group which is substituted by an alkyl group. The alkyl group can be substituted by halogen. Preferred examples are methylsulfonyl and trifluoromethylsulfonyl.

[0015] The term "arylsulfonyl" means alone or in combination a sulfonyl group which is substituted by an aryl group. Preferred is the tosyl group.

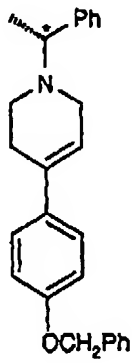
[0016] The term "salts" means compounds which are formed by reaction of compounds of formula 1 with inorganic

acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. The term salts includes solvates and particularly hydrates of such salts.

[0017] The term "halogen" means fluorine, chlorine, bromine, iodine and preferably chlorine and bromine. Most preferred is chlorine.

[0018] The term "anion" means an atom, a group of atoms or a molecule with negative charge. This charge can be a single or a multiple charge. Examples of anions are the halogen anions, SO_4^{2-}, PO_4^{3-}. Particularly preferred is the Cl- anion.

[0019] The term "asymmetric carbon atom (C*)" means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog-Convention the asymmetric carbon atom can be of the "R" or "S" configuration. A preferred example for an asymmetric carbon atom C* is shown in the formula



wherein the asymmetric carbon atom C* is of the R configuration.

[0020] The term "-O-" in groups such as -O-alkyl, -O-cycloalkyl, -O-alkenyl, -O-aryl, -O-benzyl, -O-aralkoxyalkyl, -O-alkylsulfonyl, -O-arylsulfonyl, means an oxygen with a free valence. For example -O-alkyl means alkoxy and -O-cycloalkyl means cycloalkoxy.

[0021] In a preferred aspect, the invention is concerned with the preparation of compounds of the formula 1, wherein R^5 is alkyl or cycloalkyl and R^1, R^2 and A are defined as above.

[0022] Also preferred is the process according to the present invention, wherein R^4 is unsubstituted phenyl or substituted phenyl and, wherein the substituents of phenyl are one or several chosen from alkyl, halogen or nitro, preferably methyl or chloro. In a particularly preferred embodiment of the above process R^4 is unsubstituted phenyl and R^1, R^2 and A are defined as above and particularly, wherein R^5 is alkyl, preferably methyl.

[0023] Particularly preferred is the process, wherein R^4 is phenyl, R^5 is methyl and R^1, R^2 and A are defined as above.

[0024] Also preferred is the process of the present invention, wherein A is substituted or unsubstituted ortho, meta or para phenylene wherein the substituents of the phenylene which are defined by formula 1 are placed ortho, meta or para to one another. The para position is preferred. The substituted phenylene has one or several additional substituents chosen from alkyl, halogene and nitro. Particularly preferred is the above process, wherein A is unsubstituted phenylene and especially unsubstituted para phenylene.

[0025] Preferred is also the process of the present invention, wherein R^2 is -O-alkyl, -O-cycloalkyl, -O-aryl, -O-benzyl or -O-aralkyl. Particularly preferred is -O-benzyl and -O-methyl. Most preferred is -O-benzyl.

[0026] Also preferred is the above process, wherein the hydroboration is effected as anyone of the hydroboration reactions which are known in the art such as achiral or chiral hydroboration reagents. Preferred examples of such compounds are $NaBH_4/BF_3 \cdot Et_2O$, BH_3-THF, BH_3-dimethylsulfide complex, BH_3-triethylamine complex, 9-borabicyclo(3.3.1)-nonane and isopinocampheyl-borane or a chemical equivalent of anyone of the mentioned compounds. Particularly preferred is the above process, wherein a compound of the formula 2 is reacted with $NaBH_4/BF_3 \cdot Et_2O$, BH_3-THF or isopinocampheyl borane. Most preferred are $NaBH_4/BF_3 \cdot Et_2O$ and isopinocampheyl borane.

[0027] Compounds of the formula 2 and their salts are new and also part of the present invention.

[0028] The preparation of compounds of formula 2 comprises reaction of compounds of formula 3 or 4

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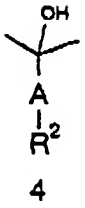

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with compounds of the formula R^1-NH_2 or a salt thereof, wherein R^1, R^2 and A are defined as before. Particularly preferred is the preparation of compounds of formula 2 which comprises reaction of compounds of formula 3 or 4 in the presence of formaldehyde or a chemical equivalent thereof.

[0029] Another preferred aspect of the present invention is the isolation of the desired stereoisomer of a compound of formula 1 by crystallisation of a salt thereof. Particularly preferred is the crystallisation of a chloride of a compound of the formula 1.

[0030] Moreover, a preferred aspect of the present invention is the above process followed by a reaction with hydrogen. Particularly preferred is the reaction of a compound of the formula 1 or a salt thereof, particularly the desired stereoisomer of a compound of the formula 1 or a salt thereof with hydrogen and especially in the presence of a catalyst such as palladium on carbon.

[0031] Another preferred aspect of the present invention is the transformation of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride to 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine characterised in that

a) (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride reacts with hydrogen to yield (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride;

b) reaction with di-tert.-butyl-dicarbonate in the presence of a base forms (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester;

c) reaction with 1-(3-chloro-propoxymethyl)-2-methoxy-benzene and potassium carbonate yields (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester;

d) reaction with 2-chloromethyl-7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalene and sodium hydride forms (3R,4R)-4-[4-(3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester;

e) reaction with hydrochloric acid yields (3R,4R)-3-(7-hydroxy-naphthalen-2-yloxymethyl)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester;

f) reaction with 1-(2-hydroxy-ethyl)-4-methyl-piperazine and triphenylphosphine yields (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester; followed by

g) a reaction with hydrogen chloride.

[0032] Also preferred is the transformation of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride to (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine characterised in that

a) (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride reacts with hydrogen to yield (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride;

b) reaction with di-tert-butyl-dicarbonate in the presence of a base forms (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester;

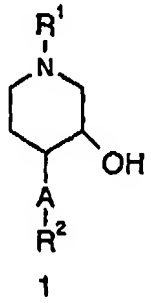
c) reaction with 1-(3-chloro-propoxymethyl)-2-methoxy-benzene and potassium carbonate yields (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy)-phenyl]-piperidine-1-carboxylic acid tert-butylester;

d) reaction with 7-bromomethyl-quinoline hydrobromide and sodium hydride to yield (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-yl-methoxy)-piperidine-1-carboxylic acid tert-butylester;

e) reaction with sodium borohydride yields (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine-1-carboxylic acid tert-butyl ester; followed by

f) a reaction with hydrochloric acid.

[0033] Compounds of the formula 1 and their salts are new and also part of the present invention:



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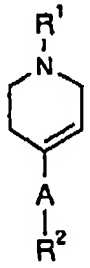
R^1, R^2 and A are defined as above. A preferred compound is (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol and salts thereof.

[0034] Compounds of the formula 2 and their salts are new and also part of the present invention:



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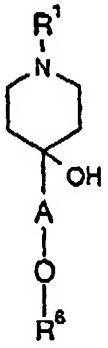
R^1, R^2 and A are defined as above. Particularly preferred is (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine and salts thereof.

[0035] Furthermore, compounds of the formula 5 and their salts are new and a part of the present invention:



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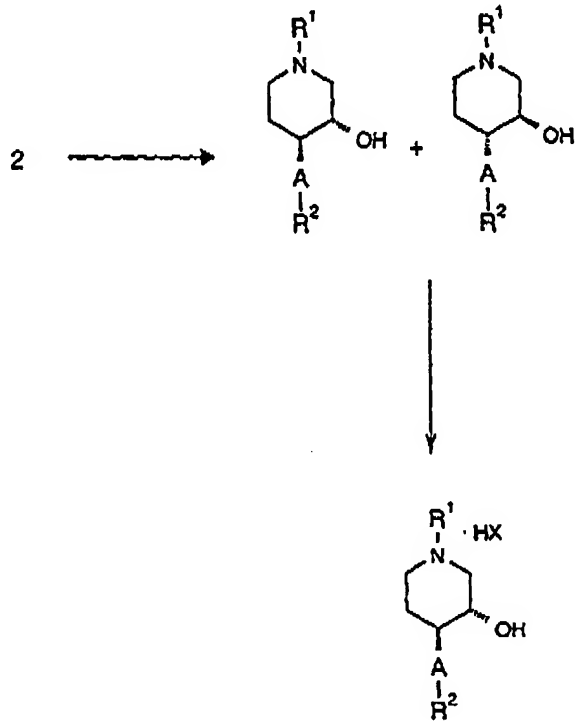
wherein R^1 and A are defined as above and R^6 is alkyl, cycloalkyl, alkenyl, aryl, aralkyl, aralkoxyalkyl, alkylsulfonyl or arylsulfonyl. Particularly preferred is (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-piperidin-4-ol and salts thereof.

[0036] The invention also relates to the use of a compound of formula 1 in the preparation of renin inhibitors, preferably 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine and (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine, wherein R^1, R^2 and A are defined as described before.

[0037] Furthermore, the invention also relates to compounds as obtained by the above process.

[0038] In more detail, the process of the invention may be described as follows:

Hydroboration of a compound of formula 2 and optionally isolation of the desired stereoisomer:



wherein R^1, R^2, A are defined as before and X is an anion, preferably Cl-.

[0039] A compound of the formula 2 can be reacted with compounds which are known for use in hydroboration reac-

tions and especially with chiral or achiral hydroboration reagents using inert solvents. Examples for such reagents are BH_3-THF, BH_3-dimethylsulfide complex, BH_3-triethylamine complex and 9-borabicyclo(3.3.1)-nonane or a chemical equivalent of anyone of the mentioned compounds. Preferred are isopinocampheylborane and particularly preferred is $NaBH_4/BF_3 \cdot Et_2O$. Also included are chemical equivalents of anyone of these compounds. Inert solvents taken alone or in combination can be used, particularly, solvents which are known for their utilisation in hydroboration reactions. Examples of such solvents are linear or cyclic ethers such as dimethylether, diethylether, tetrahydrofuran, dioxane, monoglyme, diglyme and mixtures of any of these solvents. A preferred solvent is dimethoxyethane.

[0040] A temperature range of from about -20°C to the boiling point of the solvent is suitable for the reaction of the present invention. The preferred temperature range is between about -20°C to about 20°C preferably from about 0°C to about 5°C.

[0041] The above reaction is followed by an oxidative work-up under basic conditions including addition of a base such as NaOH and an oxidising agent for example perborate or preferably H_2O_2.

[0042] The temperature range for the addition of the base and the oxidising agent is from about -20°C to the boiling point of the solvent. A preferred temperature range for the addition of the base is from about 0°C to about 10°C and especially from about 5°C to about 10°C. the reaction mixture is treated with the oxidising agent preferably at temperatures ranging from about 20°C to about 60°C and particularly from 30-50°C. However, lower or higher temperatures may be used.

[0043] According to the above process compounds of formula 1 are formed as a mixture of stereoisomers and particularly as a mixture of diastereomers or only one of the diastereomers is formed. In a preferred aspect one of the diastereomers is formed preferably.

[0044] In a preferred embodiment of the invention (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydropyridine yields a mixture of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol and (3S,4S)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol and particularly wherein the products are formed in a ratio of about 3 : 1.

[0045] Optionally the desired diastereomer can be isolated by methods known in the art such as crystallisation, chromatography or distillation. These methods also include the formation of salts or derivatives of compounds of the formula 1 and in a second step the separation of these salts or derivatives by crystallisation, chromatography or distillation etc. These methods, especially methods for the separation of diastereoismers are well known in the art and are for example described in Houben-Weyl, Methods of Organic Chemistry.

[0046] A preferred method of isolation is the crystallisation of the salts of compounds 1. Especially preferred acids which can be used for the formation of salts of compounds of the formula 1 are for example hydrohalic acids, preferably HCl.

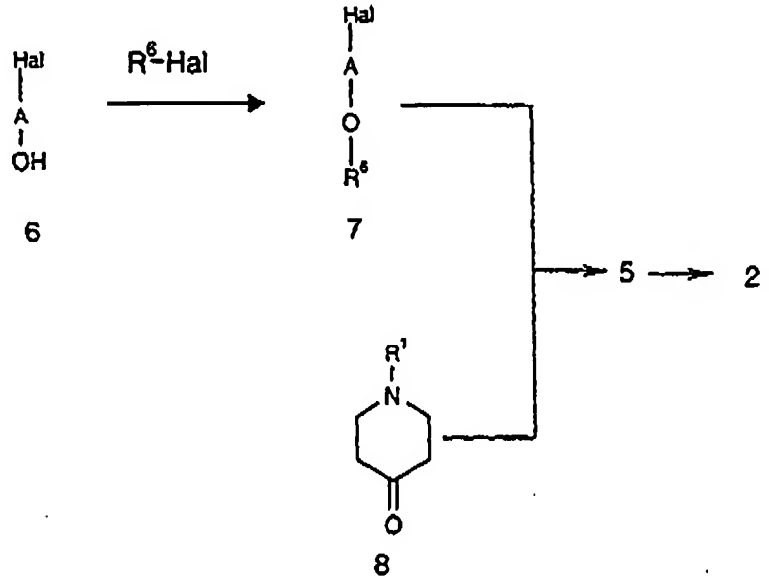
[0047] Preferred solvents which can be used for the crystallisation of compounds of formula 1 and particularly of salts of compounds of formula 1 are protic or aprotic solvents which do not react with compounds of formula 1. Especially preferred are ethanol, methanol or their mixtures with pentane or hexane.

[0048] One preferred embodiment of the isolation of the desired stereoisomer is the crystallisation of hydrochlorides of compounds of formula 1 in solvents such as ethanol or isopropanol and particularly in methanol.

[0049] After isolation the desired stereoisomer, especially diastereomer, can be reacted with hydrogen especially in the presence of a catalyst such as palladium on carbon or any other catalyst which might be suitable in the hydrogenolytic removal of groups such as benzyl. Preferred solvents for this reaction are for examples alcohols, water or acetic acid taken alone or in combination. Particularly preferred is the mixture of methanol and water. Then the obtained compound can be transformed by the reaction with di-tert-butyl-dicarbonate, preferably in the presence of a base such as triethylamine. A preferred solvent for this reaction is for example methanol. Moreover, this compound can be used in the preparation of renin inhibitors as disclosed in WO 97/09311. In general, this preparation can be performed as follows: The selective functionalization of the phenolic function can be performed with alkylation reactions using aliphatic or benzylic chlorides, bromides, iodides, tosylates or mesylates in the presence of a base like potassium carbonate in solvents such as an ether like tetrahydrofuran, dimethylformamide, dimethylsulfoxide, acetone, methyl-ethyl-ketone, or pyridine at temperatures between 0°C and 140°C. The alkylating agents used can either contain the whole chain desired or optionally suitably protected functional groups which allow further structural modifications at a later stage of the synthesis. Functionalization at the secondary hydroxy function of the piperidine ring can then be performed in solvents as ethers like tetrahydrofuran or 1,2-dimethoxyethane, or in dimethylformamide or dimethylsulfoxide in the presence of a base like sodium hydride or potassium tert-butoxide and a suitable alkylating agent, preferentially an aryl methyl chloride, bromide, mesylate or tosylate at temperatures between 0°C and 40°C. The alkylating agents used can either contain the whole substituent desired or optionally suitably protected functional groups which allow further structural modifications at a later stage of the synthesis. Further structural variations can comprise removal of protective functions followed by functionalizations of the liberated functional groups, e.g. etherification of a phenolic moiety. But also reduction of e.g. a quinoline unit to a tetrahydroquinoline unit by e.g. sodium borohydride, nickel chloride in solvents like methanol or ethanol. Final removal of the Boc-protective group can be performed in the presence of acids such as

hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic acid in a variety of solvents such as alcohols and alcohol/water mixtures, ethers and chlorinated hydrocarbons. The Boc-protective group can also be removed with anhydrous zinc bromide in inert solvents such as dichloromethane.

[0050] The preparation of the start compounds of formula 2 can be represented by the following scheme:



In detail, a compound of formula 2 can be obtained by the reaction of compound 5 with an acid, e.g. oxalic acid in an inert solvent wherein compounds 5 are formed by reacting a compound of the formula 7 in an inert solvent with butyllithium or a Grignard reagent to form an organometallic intermediate which is reacted with a compound of the formula 8. The preparation of compound 7 can be performed by reacting a compound of the formula 6 with a compound of the formula R^6-Hal in the presence of a base and preferably a catalyst such as NaI in an inert solvent. R^6 is alkyl, cycloalkyl, alkenyl, aryl, aralkyl, aralkoxyalkyl, alkylsulfonyl or arylsulfonyl. Compound 8 is obtainable for example by the reaction of R^1-NH_2 with 1-ethyl-1-methyl-4-oxo-piperidinium iodide in the present of a base. 1-Ethyl-1-methyl-4-oxo-piperidinium iodide is obtainable by the reaction of 1-ethyl-4-piperidone with methyl iodide in an inert solvent.

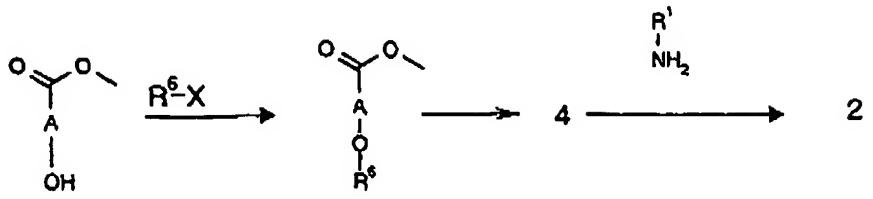
or

[0051] Alternatively, a compound of formula 2 can be obtained by the reaction of an ammonium salt R^1-NH_3+X- with formaldehyde and compound 3 which can be obtained e.g. by a Wittig reaction of the appropriate phosphorane with compound 9 in an inert solvent.

or

[0052] Alternatively, a compound 2 can be prepared by the reaction of an ammonium salt of the formula R^1-NH_3+X- with formaldehyde and with a compound of the formula 4. Compound 4 is formed by the reaction of an organometallic compound containing a methyl group attached to the metal as in methylmagnesium bromide or methyllithium with compound 9, while compound 4, wherein R^2 means chlorine, bromine or iodine can be prepared via oxidation of a halocumene (for example described in US 3954876 or DE 2302751).

or



10 11

[0053] Alternatively compounds of formula 2 are obtainable by reacting a salt of the formula R^1-NH_3X with formaldehyde and compound 4. Preferably, R^1-NH_3X is generated in the reaction mixture from a compound R^1-NH_2 using the appropriate amount of a suitable acid HX. Furthermore, compound 4 can be obtained by the reaction of compound 11 with an adequate organometallic compound. Moreover, compound 11 is formed by the reaction of compound 10 with R^6-X in the presence of a base in an inert solvent. R^6 is defined as above.

[0054] The following preparations and examples illustrate preferred embodiments of the present invention but are not intended to limit the scope of the invention.

Example 1

(Preparation of product)

[0055]

a) Preparation of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol

The reaction flask was charged under argon with 60 g (162mmol) of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine and 600mL of dimethoxyethane. After addition of 9.2 g (243mmol) of sodium-borohydride the mixture was cooled to 0°C under stirring. Then 45.9 g (323mmol) of borontrifluoride-diethyletherate was added during 40 min, wherein the temperature was kept at 0-5°C. The reaction mixture was stirred at 5°C for additional 2 h and then at room temperature for 165 min. After cooling to 0°C, 350mL of 4 N NaOH was added during 1 h, wherein the temperature was kept at 5 - 10°C. Then 60mL of 30% H_2O_2 was added at 20°C during 1 h. After additional stirring for 20 min the mixture was heated to 45°C, which caused the temperature to raise temporarily to 55°C. After cooling, the temperature was kept at 45°C for a total of 3h. After stirring overnight at room temperature the reaction mixture was poured into a mixture of 1 L half-saturated NaCl solution and 800mL of ethyl acetate. After extraction with ethyl acetate the organic phases were washed with water and dried over Na_2SO_4. After concentration 67.4 g of the diastereomeric mixture of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol and (3S,4S)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol were obtained in a ratio of 3 : 1.

b) Isolation of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol-hydrochloride

25mL of 37% HCl were added over 30 min to 80mL of ethanol at 5°C. This mixture was added under stirring at 15°C during 1 h to a solution of 67.4g of the product mixture obtained by reaction a) in 300mL of ethyl acetate. Crystals began to form after addition of 1/3 of the above ethanolic / HCl solution. The mixture was stirred for 4 h at 0°C and then 100mL of pentane was added and stirring was continued for 1 h at 0°C. The crystals were separated, washed with pentane (2 x 50mL) and dried in vacuo. 61.5g of crude hydrochlorides of the diastereomeric alcohols was obtained. The hydrochlorides were dissolved at 60°C in 260mL methanol and were crystallised overnight under stirring and cooling down to room temperature. The crystals were separated, washed with ethanol (2 x 50mL) and pentane (2 x 80mL) and dried in vacuo. 38.3 g of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol-hydrochloride was obtained as white crystals.

Example 2

(Preparation of product)

[0056]

a) Preparation of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol

The reaction flask was charged under argon with 4mL of a 0.75 M solution of isopinocampheyl-borane ($IpcBH_2$ derived from (+)-α-pinene) in THF. 1mmol of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine was added and the mixture was stirred for 16 h at 22°C. The work-up of the reaction mixture included treatment with acetaldehyde and alkaline H_2O_2 and was carried out in analogy to the method described by H.C. Brown et al. (*J. Org. Chem.* 1987, *52*, 310) for this type of hydroboration. Chromatography of the crude product afforded 240mg of a mixture of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol and (3S,4S)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol in a ratio of 85:15.

b) Separation of the desired stereoisomer can be performed as described in example 1b).

Example 3

(Preparation of starting material)

[0057]

a) Preparation of 4-benzyloxybromobenzene

200 g (1.16mol) of 4-bromophenol was dissolved in 2.1 L acetone under argon. Then 320 g (2.31mol) K_2CO_3 and 3.465 g (23.1 mmol) NaI were added. The mixture was stirred at room temperature and 292.7 g (2.31mol) of benzyl chloride was added during 1h. Then the mixture was boiled during 48 h. The acetone (ca. 500mL) was partially removed on the rotary evaporator. 1.2 L 10 % aq. Na_2CO_3 was added to the residue. After extraction with ethyl acetate (1x1 L + 2x500mL) the organic phase was washed with 1 L of a half-saturated NaCl solution. After drying over Na_2SO_4 and concentrating, the main part of the benzyl chloride was removed. 400mL of pentane was added to the residue. The crystallisation began during stirring at 0°C. The crystals were separated and washed with 2x150mL pentane and dried during 2 h at 15 mbar (40C° bath temperature) and 2 h under high vacuum at room temperature. 230 g (75 %) 4-benzyloxybromobenzene was obtained.

b) Preparation of 1-ethyl-1-methyl-4-oxo-piperidinium-iodide

To a solution of 93 g (730mmol) 1-ethyl-4-piperidone (Aldrich 27950-1) in 730mL acetone 124 g (876mmol) methyl iodide (Acros 12237) was added during 30 min. The temperature was kept at 25-30°C. The product began to precipitate after addition of 1/5 of the methyl iodide. The mixture was stirred for 5h at 22°C and 30 min at 0 °C. The cold suspension was filtered and the product was washed with acetone. 188 g (95 %) 1-ethyl-1-methyl-4-oxo-piperidinium iodide was obtained.

c) Preparation of (R)-1-(1-phenyl-ethyl)-piperidin-4-one

a) Under argon 84.6 g (698mmol) (R)-(+)-1-phenylethylamine (Merck no. 807031) and 1.4 L ethanol were mixed. A solution of 203 g (1.47mol) K_2CO_3 in water was added. The mixture was heated at 80°C under stirring and a solution of 188 g (698mmol) 1-ethyl-1-methyl-4-oxo-piperidinium iodide in 700mL water was added during 1h. The mixture was heated again for 105min under stirring and then ethanol was removed on the rotary evaporator.

The residue was extracted with dichloromethane (1x1.5 L + 1x1 L). The organic phases were washed with half-saturated NaCl solution (2x800mL) and dried with Na_2SO_4. After evaporation of the solvent 144 g crude (R)-1-(1-phenyl-ethyl)-piperidin-4-one was obtained. 70mL 37 % HCl were added at 5°C to 300mL of isopropanol during 30 min. The mixture was added during 2 h under stirring at 15-20°C to a solution of 144 g crude (R)-1-(1-phenyl-ethyl)-piperidin-4-one in 100mL ethylacetate. Crystallisation began after addition of 1/3 of the above mixture. The suspension was stirred overnight at room temperature and then for 3 h at 0°C. After adding 80mL of pentane the mixture was stirred again for 3 h at 0°C. The product was separated and washed with isopropanol (3x70mL). After drying the hydrochloride (188 g) was suspended in 1 L dichloromethane and 700mL of 10 % Na_2CO_3 was added. The organic phase was separated and washed with half-saturated NaCl (1x1L). After drying over $MgSO_4$ the organic phase was concentrated. The residue was dried during 2 h in high vacuum. 113 g (R)-1-(1-phenyl-ethyl)-piperidin-4-one was obtained.

d) Preparation of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-piperidin-4-ol

Under argon 175.2 g (666mmol) 4-benzyloxybromobenzene was dissolved in 1.4 L dry THF (MS 4 A). The solution was cooled to -75°C and a solution of 416mL 1.6 M butyllithium (666mmol) in hexane was added during 40 min. After stirring for 1 h a solution of 113 g (555mmol) (R)-1-(1-phenyl-ethyl)-piperidin-4-one in 400mL dry THF was added during 1 h at -75°C. The mixture was stirred for another 1 h and, after heating to room temperature, poured into 1.5 L of ice water. The mixture was extracted with 1 L ethyl acetate. The organic phase was washed with 1 L of a half-saturated NaCl solution, dried over Na_2SO_4 and concentrated. 262 g of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-piperidin-4-ol was obtained.

e) Preparation of (R)-4-(4-Benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydropyridine

121.7 g crude (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-piperidin-4-ol was dissolved at 40°C in 1.21 L dichloroethane. 59.4 g (471mmol) oxalic acid (Merck 492) was added. The mixture was boiled for 3 h, while 20mL of water was separated. The reaction mixture was washed at room temperature with 1.2 L 10 % Na_2CO_3. The precipitate (52 g) was separated from filtrate A and added to a mixture of 250mL 2 N NaOH and 300mL dichloromethane, where it was dissolved after stirring for 30 mm at 30-35°C. The organic phase was separated and washed with a half-saturated NaCl solution. The obtained precipitate was separated and dissolved in 200 mL dichloromethane and 60mL methanol. The combined organic phases were concentrated after drying over Na_2SO_4. 80mL ethyl acetate was added to the residue and stirred for 2 h. The crystals were separated, washed with pentane, and dried. 36.5 g of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydropyridine was obtained.

The organic phase of the above-mentioned filtrate A was washed with 1.5 L of a half-saturated NaCl solution. After drying the organic phase was concentrated. 80mL ethyl acetate and 30mL ether were added to the residue. After stirring for 3 h at 0°C the crystals were separated and then washed with ethylacetate (2x20mL) and pentane (50mL) and dried. 33.0 g of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydropyridine was obtained.

In total: 33.0 g + 36.5 g = 69.5 g (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydropyridine (73 % based on (R)-1-(1-phenyl-ethyl)-piperidin-4-on) was obtained.

Example 4

(Preparation of starting material)

[0058]

a) Preparation of 2-(4-benzyloxy-phenyl)-propen-2

At room temperature 29.6 g of methyltriphenylphosphonium bromide (83mmol) was suspended in 75mL of tetrahydrofuran. A solution of 9.2 g of potassium tert-butoxide (82mmol) in 35mL of tetrahydrofuran was added over 30 min, and the mixture was stirred for 10 min, at room temperature and was then cooled to 0°C. At this temperature, a solution of 17.0 g of 4-benzyloxyacetophenone (75mmol) in 100 mL of tetrahydrofuran was added during 1.5 h to the solution of the ylide. Stirring at 0°C was continued for 1 h, then 1 mL of acetic acid was added to the reaction mixture. The reaction mixture was poured into a mixture of 300mL of saturated aq. sodium bicarbonate, 200 g of ice and 250mL of ethyl acetate. Then the aqueous phase was extracted with ethyl acetate. The organic phases were washed with 200mL of 20% aq. sodium chloride, combined, dried (Na_2SO_4) and evaporated under reduced pressure to give 40.5 g of a white solid residue. The residue was suspended in 250mL of hexane, and the mixture was stirred overnight at room temperature. The tripenylphosphinoxide was filtered off and washed with hexane. The filtrate was evaporated to give 15.8 g of a white solid. In order to remove traces of triphenylphosphine oxide, the product was passed through a pad of silica gel using hexane-ethyl acetate 95:5 (750mL) as eluent. The combined fractions containing the desired compound were evaporated. The residue was suspended in 80mL of pentane, then the product was collected by filtration, washed with pentane and dried to a constant weight. 14.1 g 2-(4-benzyloxy-phenyl)-propen-2 was obtained.

b) Preparation of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine

At room temperature 20.7 g of (R)-1-phenylethylamine hydrochloride (131mmol) was dissolved in 60mL of water. 22mL of 36.5 % aqueous formaldehyde was added and the mixture was stirred 10 min at room temperature and then warmed up to 40°C. At this temperature, a solution of 26.75 g of 2-(4-benzyloxy-phenyl)-propen-2 (119mmol) in a mixture of 30mL of dioxane and 74mL of dichloromethane was continuously added over 1.25 h. During and after the addition of the olefin solution, dichloromethane was distilled off. After the removal of dichloromethane, the reaction mixture was stirred at 70°C overnight. A solution of 9.96g of conc. sulphuric acid (99mmol) in 30mL of water was added during 5 min to the reaction mixture which was then heated to 95-100°C and stirred at this temperature for 5.5 h. The reaction mixture was slowly poured into a mixture of 250mL of 10 % aq. sodium car-

bonate and ice and then extracted with 600mL of dichloromethane. The organic phases were extracted with one portion of 600mL of 20 % aq. sodium chloride, combined, dried (Na_2SO_4) and evaporated under reduced pressure to give 64 g crude product as a brown-red oil which partially crystallised. The crude product was dissolved in 250mL of dichloromethane. 120mL of isopropanol was added and the dichloromethane as well as a small part of the isopropanol was distilled off at reduced pressure (rotary evaporator, bath 45°C). White crystals started to precipitate, and the suspension was stirred at 0°C for 2 h. The crystals were collected on a filter funnel and washed with three portions of 50mL of cold isopropanol and with 60mL of hexane. 29.2 g (66%) (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine was obtained after drying for 2 h at 16 mbar/50°C and for 2 h at 0.2 mbar/22°C.

Example 5

(Preparation of starting material)

[0059]

a) Preparation of 2-(4-benzyloxy-phenyl)-propan-2-ol

The reaction flask was charged under argon with 3.45 g of magnesium (142mmol). A solution of 21.16 g of methyl iodide (147mmol) in 120mL of tert-butyl-methyl-ether was added during 45 mm at 45 °C under stirring. Then stirring was continued for 1 h at 45 °C and then a solution of 27.12 g of 4-benzyloxyacetophenone (120mmol) in 100mL of tetrahydrofuran was added during 45 min, while a temperature of 45°C was again maintained. Stirring at 45 °C was continued for 1.5 h. After cooling to room temperature, the white suspension was poured into a mixture of 100mL of 10% aqueous ammonium chloride and of ice and extracted with 150mL of ethyl acetate. The aqueous phase was separated and extracted with 100mL of ethyl acetate. The organic phase was washed with 120mL of 20% aq. sodium chloride, combined, dried ($MgSO_4$) and evaporated under reduced pressure to give 29.9 g of crude product as an oil which partially crystallised. The crude product was taken up in 30mL of dichloromethane. The solution was concentrated at the rotary evaporator almost to dryness. Then 6mL of ethyl acetate was added followed by gradual addition of a total of 180mL of hexane. The suspension was then kept at 0°C for 30 min. The crystals were collected and washed with cold hexane. After drying for 2h at 16 mbar/45°C 26.7 g (92%) 2-(4-benzyloxy-phenyl)-propan-2-ol was obtained.

b) Preparation of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine

At room temperature 6.94 g of (R)-1-phenylethylamine hydrochloride (44mmol) was dissolved in 24mL of water. 8.0 g of 36.5 % aqueous formaldehyde (2.92 g HCHO, 97mmol) was added and the mixture was stirred for 10 min. Then, a solution of 9.68 g of 2-(4-benzyloxy-phenyl)-propan-2-ol (40mmol) in 10mL of dioxane was added. The reaction mixture was heated to 70°C and stirred overnight at this temperature. A solution of 1.72 g of conc. sulphuric acid (17.6mmol) in 8mL of water was added to the reaction mixture within 5 min. Then the mixture was heated to 100 °C and stirred at this temperature for 7 h. The reaction mixture was slowly poured into a mixture of 150mL of 10% aq. sodium carbonate and 50 g of ice and extracted with 450mL of dichloromethane. The organic phases were extracted with 150mL of water, combined, dried (Na_2SO_4) and evaporated under reduced pressure to give 18.1 g crude product as a orange-red oil which partially crystallised.

The crude product was dissolved in 60mL of dichloromethane. 80mL of isopropanol was added and the dichloromethane as well as a small part of the isopropanol was distilled off at 400 mbar (rotary evaporator, bath 55°C). White crystals precipitated, and the suspension was stirred 1 h at room temperature and additionally 1 h at 5°C. The crystals were collected and washed with 2 portions of 25mL isopropanol and with 2 portions of 25 mL hexane. The product was then dried for 2 h at 16 mbar/40°C and for 3 h at 0.2 mbar/22°C. 9.1 g (61%) of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine was obtained.

c) Preparation of (R)-1-phenylethylamin hydrochloride

At room temperature 122 g of (R)-1-phenylethylamine (1.0mol) was dissolved in 30mL of isopropanol. The solution was stirred and cooled to 0°C. Then, a previously prepared solution of 100mL of 37 % hydrochloric acid (118 g, 1.2mol) in 320mL of isopropanol was added during 1 h. The solution was stirred at 0 °C for an additional 40 min, and then it was concentrated on a rotary evaporator (16 mbar, bath 45°C) to a volume of 300mL. The translucent gel which had formed was transferred into a 1.5 l flask, then, under stirring, 250mL tert-butyl-methyl-ether was slowly added. Crystals started to form and the suspension was stirred at 0°C for 3 h. The product was collected by filtration, washed with 100mL of tert-butyl-methyl-ether and dried at 30°C/16 mbar for 4 hours. 133 g (84 %) of 1-phenylethylamine hydrochloride was obtained.

Example 6

(Preparation of starting material)

[0060]

a) Preparation of methyl-4-benzyloxybenzoate

To a solution of 15.2 g of methyl-4-hydroxybenzoate (100mmol) in 125mL of N,N-dimethylformamide was added under stirring 33.13 g of potassium carbonate (240mmol). Then 17.45 g of benzyl bromide (102mmol) was added within 5 min. The mixture was stirred at 25°C using a water bath. The reaction was complete after 3h. The reaction mixture was poured into a mixture of 180 g of ice and 200mL of ethyl acetate. After extraction, the aqueous phase was separated and extracted with three portions of 80 mL of ethyl acetate. The organic phase was washed with two portions of 150mL of water, combined, dried ($MgSO_4$) and partially concentrated to give a thick suspension. 60mL of pentane was added and the suspension was stirred during 2 h at room temperature. The crystalline methyl 4-benzyloxybenzoate was collected on a filter, washed with pentane and dried.

b) Preparation of 2-(4-benzyloxy-phenyl)-propan-2-ol

Under argon 6.63 g of magnesium (273mmol) was suspended in 15mL of tert-butyl methyl ether. A solution of 38.68 g of methyl iodide (273mmol) in 145mL of tert-butyl methyl ether was added during 45 min under stirring while maintaining the temperature at 40°C. Then stirring was continued at 40°C for 1.5 h and then the mixture was cooled to room temperature. A solution of 30.0 g of methyl 4-benzyloxybenzoate (124mmol) in 120mL of tetrahydrofuran was then added during 1 h. The temperature was kept at 20°C. After complete addition, the reaction mixture was heated to 42°C and stirred 3 h at this temperature. After cooling to room temperature, the reaction mixture was poured into a mixture of 300mL of 10 % aqueous ammonium chloride and 100 g of ice and extracted with ethyl acetate. The organic phases were washed with water and saturated aqueous sodium bicarbonate, combined, dried and evaporated to give the crude product as an oil which partially crystallised. The product was dissolved at 25°C in diethyl ether. When crystals started to separate the solution was cooled to 18°C. After 30 min hexane was added. The suspension was then stirred for 1 h at 5°C. The crystalline 2-(4-benzyloxy-phenyl)-propan-2-ol was collected on a filter and washed with hexane.

c) Preparation of (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine

At room temperature, the reaction flask was charged with 10.66 g of (R)-1-phenylethylamine (88mmol) and 40mL of water. Under stirring, the pH of the mixture was adjusted to a value of 4.1 by slow addition of aqueous hydrochloric acid. Then 16.0 g of 36.5 % aqueous formaldehyde (5.84 g HCHO, 194mmol) was added and the mixture was stirred for 10 min. A solution of 19.38 g of 2-(4-benzyloxy-phenyl)-propan-2-ol (80mmol in 20mL of dioxane) was then added. The reaction mixture was heated to 70°C and stirred overnight at this temperature. A solution of 3.44 g of conc. sulphuric acid (35mmol) in 16mL of water was added during 5 min. to the reaction mixture which was then heated to 100°C and stirred at this temperature for 7 h. The reaction mixture was slowly poured into a mixture of 300mL of 10% aq. sodium carbonate and 100 g of ice and extracted with dichloromethane. The organic phases were extracted with water, combined, dried and evaporated to an orange-red oil which partially crystallised. The crude product was dissolved in 120mL of dichloromethane. 160mL of isopropanol was added and the dichloromethane as well as a part of the isopropanol was distilled off at 400 mbar (rotary evaporator, bath 55 °C). White crystals precipitated. The crystals were collected on a filter funnel and washed with isopropanol and then with hexane. The obtained (R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine was then dried for 2 h at 16 mbar/40°C and for 3 h at 0.2 mbar/22°C.

Example 7

(Preparation of a precursor for renin inhibitors)

[0061]

a) Preparation of (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol-hydrochloride

The reaction flask was charged under argon with 250 mg of 10% carbon-palladium (Degussa E-101 N/D), then a solution of 5 g (11.8mmol) of (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride in 50mL of methanol and 5mL water was added. After hydogenation during 6 h at room temperature and normal pressure the catalyst was separated by filtration and washed with methanol. The filtrate was concentrated and the remaining water was azeotropically removed at the rotary evaporator using toluene (3 x 100mL). 2.7 g of (3R,4R)-

4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride was obtained as white crystals.

b) Preparation of (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester

2.5 g of (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride was dissolved in 33mL of methanol. Then 2.3 g of triethylamine was added and the mixture was cooled to -18°C. A solution of 2.6 g (11.9mmol) di-tert.-butyl-dicarbonate in 16mL of methanol was added during 30 min. The reaction mixture was stirred for 1 h at -18°C and then heated slowly to 0°C. After stirring for additional 2 h at 0°C 10mL of water was added and the methanol was removed with the rotary evaporator. The residue was dissolved in a mixture of dichloromethane / water and a solution of 10% $NaHSO_4$ was slowly added. After extraction the organic phase was washed with a $NaHCO_3$ solution and with a half-saturated NaCl solution. The water phase was extracted twice with dichloromethane. The crude product was obtained after drying ($MgSO_4$) and concentrating the organic phases. Then diethylether was added and the product started to crystallise. After adding pentane the mixture was placed in the refrigerator. The next day the crystals were separated, washed with pentane and dried into vacuo. 3.1 g of (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester was obtained as white crystals.

Example 8

Preparation of 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine

[0062]

a) A solution of 16.50 g (56.24mmol) of (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-1-carboxylic acid tert-butylester in 40ml of dimethylformamide was treated in succession with 12.68 g (59.06mmol) of 1-(3-chloro-propoxymethyl)-2-methoxy-benzene (WO 97/09311) and 12.44 g (89.99mmol) of potassium carbonate. This mixture was stirred at 120°C for 26 hours. Subsequently, it was filtered, concentrated to a few millilitres, poured into 300 ml of an ice/water mixture and extracted three times with 100 ml of methylene chloride each time. The combined organic phases were washed once with a small amount of water, dried over magnesium sulphate, evaporated under reduced pressure and dried in a high vacuum. The thus-obtained crude product (31.64 g) was separated on silica gel using a 99:1 mixture of methylene chloride and methanol as the eluent and yielded 25.4 g (95.8 % of theory) (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester as a slightly yellow oil; MS: 489 ($M+NH_4^+$).

b) 25.4 g (53.86mmol) of (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester and 17.78g (55.06mmol) of 2-chloromethyl-7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalene (WO 97/09311) were dissolved in 180 ml of dimethylformamide under argon and then 2.49 g (57.09mmol) of sodium hydride dispersion (55% in mineral oil) was added. Subsequently, the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured onto ice-water, the product was extracted 3 times with methylene chloride, the organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There were thus obtained 36.43 g (89.2 % of theory) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester as a yellowish oil; MS: 759 $(M+H)^+$.

c) 36.43 g (48.06mmol) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester was placed in 700 ml of abs. methanol at 0°C, then 48 ml (96.1mmol) of hydrochloric acid in methanol (2.0 molar) was added dropwise at 5°C max. and thereafter the mixture was warmed to room temperature. After 120 minutes the reaction mixture was poured into ice-cold sodium hydrogen carbonate solution and the product was extracted three times with methylene chloride. The organic phases were washed once with distilled water, then dried over magnesium sulphate, filtered and concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There were thus obtained 28.06 g (93 % of theory) (3R,4R)-3-(7-hydroxy-naphthalen-2-yloxymethyl)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester as a light yellow amorphous solid; MS: 645 ($M+NH_4^+$).

d) A mixture of 10.15 g (16.17mmol) of (3R,4R)-3-(7-hydroxy-naphthalen-2-yloxymethyl)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester, 2.80 g (19.42mmol) of 1-(2-hydroxy-ethyl)-4-methyl-piperazine [J. Pharm. Sci. (1968), 57(3), 384-9] and 5.51 g (21.01mmol) of triphenylphosphine were dis-

solved in 450 ml of tetrahydrofuran. Then, a solution of 4.75 g (20.22mmol) of di-tert-butyl azodicarboxylate in 50 ml of tetrahydrofuran was slowly added to the reaction mixture at 0°C and stirring continued for 2 hours at room temperature. The reaction mixture was concentrated in a water-jet vacuum. The thus-obtained crude product was chromatographed on silica gel with methylene chloride and methanol. There was thus obtained 9.18 g (75.3 % of theory) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester as a colourless oil; MS: 754 $(M+H)^+$.

e) A solution of 9.15 g (12.14mmol) (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester in 250 ml of methanol was treated at room temperature with 36.41 ml of a 2.0 M solution of hydrogen chloride in methanol and the mixture was stirred at 50°C for 4 hours. Subsequently, the solution was evaporated under reduced pressure and the residue was partitioned between 200 ml of saturated sodium carbonate solution and 150 ml of methylene chloride. The aqueous phase was again extracted twice with 100 ml of methylene chloride; thereafter the organic phases were combined, dried over sodium sulphate and evaporated under reduced pressure. For purification, the crude product was chromatographed on silica gel using a 90:10 mixture of methylene chloride and methanol as the eluent. There were obtained 5.25 g (66 % of theory) of 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxyl-ethyl]-4-methyl-piperazine as a amorphous, colourless solid; MS: 654 $(M+H)^+$.

Example 9

Preparation of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine

[0063]

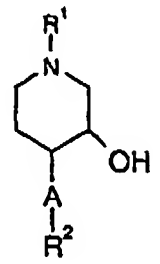
a) 3.40 g (7.20mmol) of (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester and 2.18 g (7.20mmol) of 7-bromomethyl-quinoline hydrobromide (1:1) [J. Am. Chem. Soc. 77, 1054(1955)], were dissolved in 50 ml of absolute dimethylformamide under argon and then 0.83 g (19.0mmol) of sodium hydride dispersion (55% in mineral oil) was added at room temperature in small portions. Subsequently, the mixture was stirred at room temperature for 16 hours. The reaction mixture was poured onto ice-water, the product was extracted 3 times with ethyl acetate, the combined organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated. The crude product (5.2 g, yellow oil) was chromatographed on silica gel with ethyl acetate/hexane 2:1 to yield 3.77 g (85.4 % of theory) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-yl-methoxy)-piperidine-1-carboxylic acid tert-butylester as a colourless oil; MS: 613 $(M+H)^+$.

b) 3.77 g (6.15mmol) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-yl-methoxy)-piperidine-1-carboxylic acid tert-butylester and 0.93 g (3.12mmol) of nickel(II) chloride hexahydrate were dissolved in 50 ml of methanol. 0.93 g (24.8mmol) of sodium borohydride was added at 0°C in small portions over a period of 30 minutes. The resulting black suspension was then stirred for 1 hour at 0°C, and 2 hours at room temperature. The reaction mixture was slowly poured into a vigorously stirred mixture of 150 ml 5% ammonium chloride solution and 400 ml of ether. After further stirring for 30 minutes, the organic phase was separated. The slightly blue aqueous phase was further extracted 5 times with ether. The combined organic phases were washed twice with distilled water, then dried over magnesium sulphate, filtered and concentrated. The crude product (3.2 g, yellow oil) was chromatographed on silica gel with ethyl acetate/hexane 1:1 to yield 2.92 g (76.9 % of theory) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine-1-carboxylic acid tert-butyl ester as a colourless oil; MS: 617 $(M+H)^+$.

c) 2.92 g (4.73mmol) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine-1-carboxylic acid tert-butylester were dissolved in 63 ml of abs. methanol, then 63 ml (126mmol) of hydrochloric acid in methanol (2.0 molar) were added at room temperature. After stirring for 150 minutes at 50°C, the reaction mixture was poured into 150 ml ice-cold 5% sodium hydrogen carbonate solution and the product was extracted five times with 100 ml methylene chloride. The combined organic phases were washed twice with 50 ml distilled water, dried over magnesium sulphate, filtered and concentrated. The crude product (2.9 g, yellow oil) was chromatographed on silica gel with methylene chloride/methanol/28%ammonium hydroxide solution 14:1:0.1 v/v/v to yield 1.90 g (77.7 % of theory) of (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine as a slightly yellow resin; MS: 517 $(M+H)^+$.

Claims

1. A process for the preparation of a compound of formula 1 or a salt thereof



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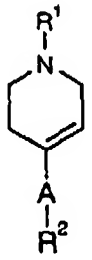
characterised in that the process comprises

a) hydroboration of a compound of formula 2



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in which formulae

A is arylene;

R^1 is $-C^*R^3R^4R^5$;

R^2 is -O-alkyl, -O-cycloalkyl, -O-alkenyl, -O-aryl, -O-aralkyl, -O-aralkoxyalkyl, -O-alkylsulfonyl, -O-arylsulfonyl, chlorine, bromine or iodine;

R^3 is hydrogen;

R^4 is aryl;

R^5 is alkyl, cycloalkyl, aryl, alkoxyalkyl or hydroxyalkyl; and,

wherein C^* is an asymmetric carbon atom;

b) optionally followed by isolation of the desired stereoisomer.

2. The process according to claim 1, wherein R^5 is alkyl or cycloalkyl.

3. The process according to claim 1 or 2, wherein R^4 is phenyl which is optionally substituted by one or more groups

independently selected from alkyl, halogen or nitro.

4. The process according to any of claims 1 to 3, wherein R^4 is phenyl and R^5 is methyl.

5. The process according to any of claims 1 to 4, wherein A is phenylene and, wherein phenylene optionally is substituted by one to four additional substituents independently selected from alkyl, halogen or nitro.

6. The process according to any of claims 1 to 5, wherein R^2 is -O-benzyl or -O-methyl.

7. The process according to any of claims 1 to 6, wherein a compound of the formula 2 is reacted with $NaBH_4/BF_3 \cdot Et_2O$, BH_3-THF or isopinocampheyl borane.

8. The process according to any of claims 1 to 7, wherein a compound of formula 2 is prepared by a process which comprises reacting a compound of formula 3 or formula 4

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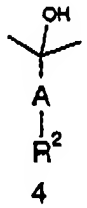

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with a compound of formula R^1-NH_2 or a salt thereof and wherein R^1, R^2 and A are defined as in claim 1.

9. The process according to any of claims 1 to 8, wherein the desired stereoisomer of a compound of formula 1 is isolated by crystallisation of a salt thereof.

10. The process according to any of claims 1 to 9 followed by a reaction with hydrogen.

11. The process according to any of claims 1 to 10, wherein a compound of formula 1 is converted to 1-[2-[7-[(3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidin-3-yloxymethyl]-naphthalen-2-yloxy]-ethyl]-4-methyl-piperazine characterised in that

a) (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride reacts with hydrogen to yield (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride;

b) reaction with di-tert-butyl-dicarbonate in the presence of a base forms (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester;

c) reaction with 1-(3-chloro-propoxymethyl)-2-methoxy-benzene and potassium carbonate yields (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester;

d) reaction with 2-chloromethyl-7-(2-trimethylsilanyl-ethoxymethoxy)-naphthalene and sodium hydride forms (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-(2-trimethylsilanyl-ethoxymethoxy)- naphthalen-

2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester;

e) reaction with hydrochloric acid yields (3R,4R)-3-(7-hydroxy-naphthalen-2-yloxymethyl)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester;

f) reaction with 1-(2-hydroxy-ethyl)-4-methyl-piperazine and triphenylphosphine yields (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-[7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-naphthalen-2-ylmethoxy]-piperidine-1-carboxylic acid tert-butylester; followed by

g) a reaction with hydrogen chloride.

12. The process according to any of claims 1 to 10, wherein a compound of formula 1 is converted to (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine characterised in that

a) (3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol hydrochloride reacts with hydrogen to yield (3R,4R)-4-(4-hydroxy-phenyl)-piperidin-3-ol hydrochloride;

b) reaction with di-tert-butyl-dicarbonate in the presence of a base forms (3R,4R)-3-hydroxy-4-(4-hydroxy-phenyl)-piperidin-1-carboxylic-acid-tert-butylester;

c) reaction with 1-(3-chloro-propoxymethyl)-2-methoxy-benzene and potassium carbonate yields (3R,4R)-3-hydroxy-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-piperidine-1-carboxylic acid tert-butylester;

d) reaction with 7-bromomethyl-quinoline hydrobromide and sodium hydride to yield (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(quinolin-7-yl-methoxy)-piperidine-1-carboxylic acid tert-butylester;

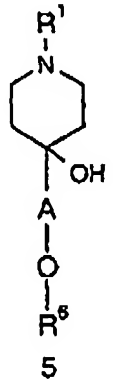
e) reaction with sodium borohydride yields (3R,4R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3-(1,2,3,4-tetrahydro-quinolin-7-ylmethoxy)-piperidine-1-carboxylic acid tert-butyl ester; followed by

f) a reaction with hydrochloric acid.

13. A compound according to formula 1 or a salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and A are defined as in any of claims 1 to 6.

14. A compound according to formula 2 or a salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and A are defined as in any of claims 1 to 6.

15. A compound according to formula 5 or a salt thereof



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wherein R^1 and A are defined as in any of claims 1 to 6 and R^6 is alkyl, cycloalkyl, alkenyl, aryl, aralkyl, aralkoxyalkyl, alkylsulfonyl or arylsulfonyl.

16. A compound according to any of claims 13, 14 and 15 selected from:

(3R,4R)-4-(4-benzyloxy-phenyl)-1-((R)-1-phenyl-ethyl)-piperidin-3-ol;

(R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-1,2,3,6-tetrahydro-pyridine;

(R)-4-(4-benzyloxy-phenyl)-1-(1-phenyl-ethyl)-piperidin-4-ol.

17. The use of a compound according to claim 13 in the preparation of renin inhibitors.

18. A compound as obtained by the process according to any of claims 1 to 10.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 11 5243

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Place of search	Date of completion of the search	Examiner
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